

TRANSLATED FROM GERMAN by
SCIENTIFIC TRANSLATION SERVICES
411 Wyntre Lea Dr.
Bryn Mawr, PA 19010

**(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE
INTERNATIONAL PATENT COOPERATION TREATY (PCT)**

- (19) **World Intellectual Property Organization**
International Bureau **PCT**
- (10) **International Publication Number**
WO 03/018075 A2
-
- (51) **International Patent Classification:** A61L 15/44
- (21) **International Application Number:** PCT/EP02/07664
- (22) **International Filing Date:** July 10, 2002 (07/10/2002)
- (25) **Language of Filing:** German
- (26) **Language of Publication:** German
- (30) **Priority Data:**
101 41 650.4 August 24, 2001 (08/24/2001) DE
- (71) **Applicant** (*for all designated states except the U.S.A.*): **LTS LOHMANN THERAPIE-
SYSTEME AG** [DE/DE]; Lohmannstrasse 2, 56626 Andernach (DE).
- (72) **Inventors; and**
- (75) **Inventors/Applicant** (*for the U.S.A. only*): **MÜLLER, Walter** [DE/DE]; Hindenburgwall
12, 56626 Andernach (DE). **HILLE, Thomas** [DE/DE]; Am Moogsberg 2 A, 56567
Neuwied (DE).
- (74) **Agent:** **SCHMIDT, Werner**; LTS Lohmann Therapie-Systeme AG, Patentabteilung [Patent
Department], Postfach 15 25, 56605 Andernach (DE).
- (81) **Designated States** (*national*): AU, BR, CA, CN, JP, KR, MX, US, ZA.
- (84) **Designated States** (*regional*): European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR).

international search report and to be protected against any receipt of the report.

For the explanation of the two-letter codes and the other abbreviation, refer to the Explanations ("Guidance Notes on Codes and Abbreviations") at the beginning of each regular issue of the PCT-Gazette.

(54) **Title:** TRANSDERMAL THERAPEUTIC SYSTEM WITH FENTANYL OR RELATED SUBSTANCES.

(57) **Abstract:** The present invention pertains to a transdermal therapeutic system (TTS), comprising a backing layer [Rücksicht in German original is a typo for "Rückschicht" meaning backing layer - Tr.Ed.], which is impermeable to the active ingredient, at least one matrix layer which contains fentanyl or an active ingredient analogous to fentanyl and is based on polyacrylate, and a protective layer to be removed before use, which system is characterized in that the polyacrylate polymer is self-adhesive, free of carboxyl groups and has a saturation solubility for fentanyl of 3 wt.% to 20 wt.%, preferably a saturation solubility of 4 wt.% to 12 wt.% and especially preferably a saturation solubility of 5 wt.% to 10 wt.%, and that the layers containing active ingredient contain at least 80 wt.% of the active ingredient incorporated in a molecularly dispersed, dissolved form.

A Transdermal Therapeutic System with Fentanyl or Related Substances

Specification

Fentanyl and substances analogous to fentanyl, such as sufentanyl, carfentanyl, lofentanyl and alfentanyl, are extremely effective analgesics. The required low dosage and their physicochemical properties, such as the *n*-octanol-water distribution coefficient, the melting point and the molecular weight make possible the transdermal administration of effective quantities of these substances, and their pharmacokinetic properties, such as the rapid metabolism and the relatively low therapeutic index make the transdermal administration desirable.

A TTS with fentanyl as the active ingredient has, indeed, been available commercially for some years. This system is a so-called reservoir system. A reservoir system is defined here as a system that contains the active ingredient in a liquid or gel-like preparation in a pouch formed from an impermeable film, which acts as a backing film, and a membrane that is permeable to the active ingredient, where the membrane is additionally provided with an adhesive layer for attaching the system to the skin. Fentanyl is dissolved in this special case in a mixture of ethyl alcohol and water. Further details of this system can be found in the US Patent Specification No. 4,588,580 and DE Patent Specification No. 35 26 339, both of which contain a more detailed description.

However, reservoir systems have the drawback that the reservoir filling containing the active ingredient comes into contact with the skin over a large area in case of a leak of the reservoir pouch and excessively high doses of the active ingredient are resorbed. This is very dangerous especially in the case of fentanyl and its derivatives, because an overdosage leads to respiratory depression and consequently fatal accidents in a short time. A number of such fatal or nearly fatal accidents were described in *Clinical Pharmacokinetics*, 2000, 38(1), 59-89.

The object of the present invention was to make available a transdermal therapeutic system with fentanyl or substances analogous to fentanyl which offers the user increased safety against the accidental absorption of overdoses.

This is achieved according to the present invention by using instead of the reservoir system a matrix system, in which the active ingredient is directly incorporated in a self-adhesive polyacrylate and thus it cannot come into contact with the skin over an area larger than that defined by the TTS even in case of damage to the system. In general, the total amount, but at least 80% of the active ingredient is dissolved in this polymer in such a system in the molecularly dispersed form, and the saturation solubility of the active ingredient in the polymer is between 3 wt.% and 20 wt.%. Furthermore, it was surprisingly found that only adhesives free of free carboxyl groups are suitable if polyacrylate adhesives are used to prepare TTS containing fentanyl and its analogs.

In the simplest case, such matrix systems comprise a backing layer, which is impermeable to the active ingredient, a self-adhesive layer containing active ingredient, and a protective layer to be removed before use. A membrane, which controls the release of the active ingredient and is normally also provided with an adhesive layer for attaching the system to the skin, is additionally present in more complicated embodiments of such systems.

The active ingredient-containing layers of such a matrix system according to the present invention

of the active ingredient in the TTS or the rate of permeation attained.

The saturation solubility of the polymer selected for the particular active ingredient is an important property of any polymer containing active ingredient in the TTS technology. This parameter is important because the thermodynamic activity of the active ingredients in the matrix depends on the ratio of the actual concentration to the saturation concentration rather than on the absolute dissolved quantity of the active ingredient in the matrix. Since the active ingredient must be distributed in the skin during the application of the TTS to the skin and activities rather than concentrations will become alike in the process, it is important for reaching the highest possible rate of permeation to select the highest possible thermodynamic activity of the active ingredient in the TTS. This means that the solubility of the active ingredient in the parts of the TTS that contain active ingredient must not be too high, because the concentration of the active ingredient in the TTS must otherwise be rather high to reach a sufficiently high thermodynamic activity. This is not advantageous if the active ingredient present at the high concentration affects the physical properties of the parts of the system that contain active ingredient and/or the active ingredient is very expensive. Both reasons apply in the case of fentanyl, and it should also be additionally borne in mind that fentanyl and its derivatives are narcotics and it is therefore desirable for that reason alone to incorporate as little active ingredient as possible in the TTS or to select the highest possible active ingredient utilization, i.e., the ratio of active ingredient released during the period during which the TTS is being used to the content in the unused TTS.

Based on this criterion, the saturation solubility of the layers containing active ingredient should not be below 3 wt.% nor higher than 20 wt.% for a three-day TTS. The active ingredient utilization becomes too low at higher saturation solubilities even at a high specific permeation rate, and the TTS does not sell well for commercial reasons because of the expensive active ingredient. The saturation solubility is between 4 wt.% and 12 wt.% and especially preferably between 5 wt.% and 10 wt.% for these reasons.

The saturation solubility of fentanyl and its analogues can be additionally reduced by the addition of substances that do not possess good dissolution properties for the active ingredient. Such substances are, e.g., liquid hydrocarbons such as dioctyl cyclohexane, liquid paraffin, hydrocarbon resins such as polyterpenes, especially polypinene, or polar substances such as glycerol, diglycerol and triglycerol or polyethylene glycols, e.g., those with a molecular weight of 200 to 1,000. These substances can form a homogeneous mixture with the polyacrylate adhesive or be contained therein as a separate phase. In particular, glycerol and its derivatives occur in the matrix as a separate phase, e.g., in the form of droplets, already at low concentrations. In particular, the higher saturation solubility in adhesives containing free hydroxyl groups can also be compensated by the addition of such substances.

Table 2 contains some data on the saturation solubility of fentanyl in some of these substances.

Table 2: Saturation solubilities of fentanyl in additives reducing the solubility.

Polyethylene glycol 400	1.5
Glycerol	< 1.5
Diglycerol	< 1.5
Diethyl cyclohexane	< 1.9
Paraffin, liquid	< 1.5

The effect of such additions can be recognized from comparative permeation studies.

The results of permeation studies with matrices based on a neutral polyacrylate adhesive containing free hydroxyl groups with and without such additives as well as of a polyacrylate adhesive without other free functional groups are compared in Table 3. All formulations contain fentanyl at a concentration of 5 wt.%.

Table 3. Comparative permeation studies with formulations with and without additives lowering the solubility.

Formulation	Cumulative quantity of permeated active ingredient [$\mu\text{g}/\text{cm}^2$] Mean value of $n = 3^*$				
	4 hr.	8 hr.	24 hr.	48 hr.	72 hr.
2	0.00	0.23	7.89	32.82	64.17
3	0.798	4.46	29.6	68.9	103.1
4	0.805	4.87	32.6	74.7	113.2

* Skin: Human epidermis, skin from female breast

Formula 2: 5 wt.% of fentanyl in a neutral polyacrylate adhesive containing 5.2% of free hydroxyl groups

Formula 3:	Fentanyl	5.0%
	Polyacrylate adhesive, neutral,	
	with 5.2% of hydroxyl groups	55.0%
	Polypinene	15.0%
	Glycerol	10.0%
	Diethyl cyclohexane	15.0%

Formula 4: 5 wt.% of fentanyl in a polyacrylate adhesive without free functional groups.

The results of the permeation study show that the rate of permeation can be significantly improved by the addition of substances that reduce the solubility of the active ingredient in the matrix. Approximately the same results are obtained with the use of an adhesive without free functional groups, which also has a low dissolving capacity for the active ingredient without additives.

The particular TTS sizes can be calculated for different TTS potencies from the permeation data. The results are listed in Table 4.

** calculated on the basis of the permeation data from Table 2

Such membranes are usually provided with an adhesive film to attach the TTS to the skin. Adhesive films based on self-adhesive polyacrylates or self-adhesive polysiloxanes are especially suitable for fentanyl and its derivatives. The advantage of polysiloxanes is that the active ingredient is very

might be used to fix TTS by the use of an additional adhesive film. However, such adhesive films may also be used in systems which contain no membranes but matrix layers with low adhesive power.

As in any TTS, it is, of course, possible in this case as well to reduce the barrier properties of the human stratum corneum by the use of permeation-enhancing substances. Such substances are, e.g., fatty acids, fatty alcohols, fatty acid esters, esters of glycerol with medium- and long-chain fatty acids and glycols such as 1,2-propanediol. All the substances that are physiologically harmless and are compatible with the active ingredient and the other inactive ingredients may be used.

It can be stated in summary that matrix systems according to the present invention show satisfactory to good rates of permeation and also make it possible to prepare TTS of an acceptable size. At the same time, the exposure of the patient to risk due to the absorption of an excessively large quantity of active ingredient as a consequence of leak is impossible. On the whole, matrix systems based on polyacrylate adhesives according to the present invention for fentanyl and its analogs represent a significant progress over the known state of the art in terms of patient safety.

1. Transdermal Therapeutic System (TTS) comprising a backing layer impermeable to the active ingredient, at least one matrix layer based on polyacrylate which contains fentanyl or an active ingredient analogous to fentanyl and is based on polyacrylate, and a protective layer to be removed before use, characterized in that the polyacrylate is self-adhesive and free of carboxyl groups and has a saturation solubility for fentanyl of 3 wt.% to 20 wt.%, preferably a saturation solubility of 4 wt.% to 12 wt.% and especially preferably a saturation solubility of 5 wt.% to 10 wt.%, and that the layers containing the active ingredient contain at least 80 wt.% of the active ingredient incorporated in the molecularly dispersed dissolved form.
2. TTS in accordance with claim 1, characterized in that the polyacrylate polymer has no free functional groups and is formed only from monomers of the acrylic acid or methacrylic acid esters and optionally additionally other polymerizable vinyl compounds without free functional groups in quantities of up to 50 wt.%, and especially vinyl acetate.
3. TTS in accordance with claim 1, characterized in that the monomer mixture on which the polyacrylate is based contains up to 20 wt.% of monomers with free functional groups in the form of 2-hydroxyethyl acrylate and/or 2-hydroxyethyl methacrylate.
4. TTS in accordance with one or more of the claims 1-3, characterized in that it additionally contains a control membrane as an additional layer.
5. TTS in accordance with claim 4, characterized in that it additionally contains a self-adhesive layer located on the membrane toward the skin for attaching to the skin.
6. TTS in accordance with claim 4 or 5, characterized in that the control membrane consists of an ethylene-vinyl acetate copolymer, expediently with a vinyl acetate content of up to 25 wt.% or a microporous film based on polyethylene or polypropylene and it expediently has a thickness of 25 μ m to 100 μ m and preferably 40 μ m to 100 μ m.
7. TTS in accordance with one or more of the claims 1-6, characterized in that the layers containing the active ingredient additionally contain substances improving the rate of permeation through human skin, especially glycols and/or those belonging to the group of the fatty acids, fatty acid esters, fatty alcohols or glycerol esters.
8. TTS in accordance with one or more of the claims 1-7, characterized in that the layers containing the active ingredient contain substances that lower the solubility of the active ingredient in these layers.
9. TTS in accordance with claim 8, characterized in that the substances lowering the solubility are hydrocarbons that are liquid at room temperature, such as dioctyl cyclohexane or liquid paraffin, hydrocarbon resins such as polypinenes resins or polyethylene glycol or glycerol.